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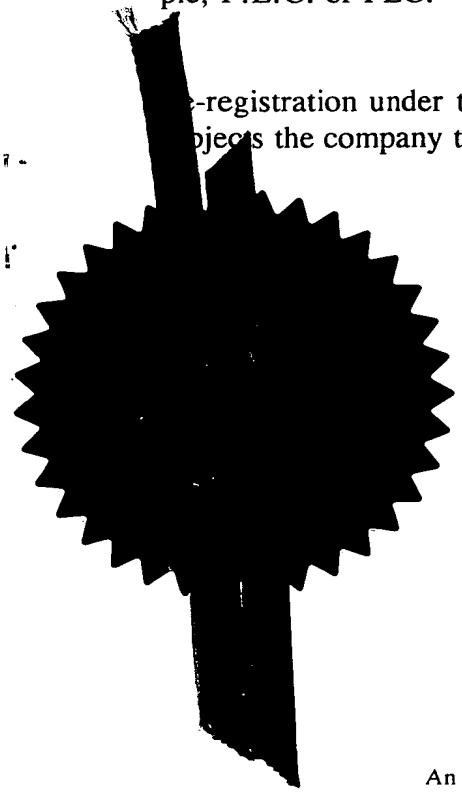

Signed Andrew Gerry

Dated 3 March 2000

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The Patent Office
Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference — REP06049GB

2. Patent application number *(The Patent Office will fill in this part)* — **9904281.4** — 24 FEB 1999

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

ReNeuron Limited
67/68 Jermyn Street
London
SW1Y 6NY
United Kingdom

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom — 7609258001

4. Title of the invention — TRANSPLANTATION

5. Name of your agent *(if you have one)* — GILL JENNINGS & EVERY

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Broadgate House
7 Eldon Street
London
EC2M 7LH

Patents ADP number *(if you know it)* — 745002

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor
b) there is an inventor who is not named as an applicant, or
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YES

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Description	7
Claim(s)	1
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Priority documents	
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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
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Any other documents *(please specify)*	

11. For the Applicant
Gill Jennings & Every

I/We request the grant of a patent on the basis of this application.

Signature

Date
24 February 1999

12. Name and daytime telephone number of person to contact in the United Kingdom

PERRY, Robert Edward
0171 377 1377

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Claims:

1. Use of a haematopoietic stem cell in the manufacture of a medicament for the treatment of a behavioural and/or psychological deficit.

2. Use according to claim 1, for intracerebral transplantation into a damaged brain.

3. Use according to claim 1 or claim 2, wherein the treatment is for Alzheimer's disease, Parkinson's disease, Korsakoff's disease or Creuzfeld-Jacob disease.

4. A method for treating brain damage comprising the intracerebral transplantation of haematopoietic stem cells into the damaged brain.

normally disperse around the injection site. They may also be implanted into ventricular spaces in the brain. If implanted into the neonate then they may disperse throughout the entire brain.

The phrase "intracerebral transplantation" used herein includes transplantation into any portion of the brain. Transplantation is not restricted to the front and larger part of the brain.

The number of cells to be used will vary depending on the nature and extent of the damaged tissue. Typically, the number of cells used in transplantation will be in the range of about one hundred thousand to several million. Treatment need not be restricted to a single transplant. Additional transplants may be carried out to further improve function.

To study the transplantation in animal models the lesion-and-behaviour model described in Sinden et al., 1995 may be used. It utilises rats in which the technique for four-vessel occlusion (4 VO), simulating human heart attack, causes relatively circumscribed and specific damage to the CA 1 pyramidal cells of the dorsal hippocampus, along with a cognitive deficit manifest as difficulty in locating a submerged and invisible platform in a swimming pool. This lesion and behaviour model provides a model of cognitive dysfunction occurring as a consequence of a common form of brain damage, i.e., transient loss of blood supply to the brain, for example, as may occur during cardiac arrest.

We have previously demonstrated that, for fetal cell-suspension transplants to restore performance in this task, they must be highly specific to the damage caused by 4VO: transplants containing CA 1 pyramidal cells are effective; transplants containing cholinergic cells from the basal forebrain, granule cells from the dentate gyrus, or even a different class of pyramidal cells (CA3) from the hippocampus are ineffective.

Methods for transplantation of cells into humans and animals are known to those in the art and are described in the literature in the art. The term "transplantation" used herein includes the transplantation of cells which have been grown <u>in vitro</u>, and may have been genetically modified, as well as the transplantation of material extracted from another organism. Cells may be transplanted by implantation by means of microsyringe infusion of a known quantity of cells in the target area where they would

with immune rejection. This requires the extraction of cells from the bone marrow of an animal.

However, the cells do not necessarily have to be conditionally immortal, and may be obtained directly from the patient to be treated.

To treat a patient it is generally of assistance to know where damage has occurred in the brain. Once the existence of damage has been established, whether it be in one isolated area or in several areas, treatment by implantation of cells into the damaged area may be carried out. In many cases, however, the location and/or type of damaged tissue may be unknown or only poorly characterised. For example, neurodegenerative diseases may lead to widespread damage to different types of cells. Treatment of such damage is still possible and is assisted by the ability of the haematopoietic stem cells to migrate extensively once transplanted and to seek out damaged tissue. The stem cells may be transplanted at a single site, or preferably at multiple sites, and may be able to migrate to the site(s) of damage and, once there, differentiate in response to the local microenvironment, into the necessary phenotype or phenotypes to improve or restore function.

After treatment the progress of the patient may be monitored using behavioural and/or psychological tests and/or, if desired, tests which monitor brain activity in selected areas of the brain. For example, tests for cognitive function may be performed before and after transplantation.

Preferably, treatment will substantially correct a behavioural and/or psychological deficit. However, that may not always be possible. Treatment according to the present invention and with the cells, medicaments and pharmaceutical preparations of the invention, may lead to improvement in function without complete correction. Such improvement will be worthwhile and of value.

chosen stage and they may be propagated for long periods. Use of conditionally immortalisation allows the development of clonal lines which are readily expandable in vitro. If the conditions under which the cells are maintained are switched to nonpermissive conditions, the development of the cells is allowed to continue. If the correct conditions are provided the cells will continue to develop and will differentiate.

Immortalised cells are usually prepared by the transduction of an oncogene into cells. There is therefore a risk of tumour formation in the long term, so such cells are not preferred for use in the present invention.

Conditionally immortal cells have the advantages of immortal cells in that they are "frozen" in the desired stage of development, are easily maintained and multiply well when under permissive conditions but they may be used in transplants as long as the environment into which they are transplanted has nonpermissive conditions. In the case of the cells of the present invention the gene used to confer conditional immortality should be chosen so that the conditions present in the brain will correspond to nonpermissive conditions.

The usual way to immortalise the cells is by transduction of an oncogene. The use of conditionally immortal cells means that under nonpermissive conditions the cells do not have oncogenic properties and so this excludes any possibility of the implantation of cells leading to tumour growth.

If non-immortal cells are used then these may be maintained in vitro in culture media with the addition of growth factors.

The gene which is used to confer conditional immortality may be incorporated into cells after extraction from the bone marrow of an animal.

The cells used in the treatment of humans should preferably be derived from human cells to reduce problems

be administered comprises conditionally immortal, haematopoietic stem cells.

The conditionally immortal cells according to, and used in, the present invention may be from clonal cell lines or may be of mixed population. Cells from clonal cell lines may be preferred. Cells from a single cell line may be used or a mixture of cells from two or more cell lines may be used.

The invention further provides a pharmaceutical preparation comprising cells according to the invention and a pharmaceutically acceptable carrier.

Description of the Invention

The present invention is based on the realisation that when haematopoietic stem cells are implanted into a damaged brain the cells surprisingly differentiate into a form of cell that is capable of repairing the damage and improve function. The phenotype of the differentiated cells may be the same as the phenotype of the damaged or lost cells, however, the differentiated cells may be of a different phenotype, or of a number of phenotypes. In any case, the cells take up a phenotype that is capable of functionally integrating and compensating for the damaged or lost cells. That is assisted by the propensity, that we have discovered, of the cells to migrate to, and seek out, damaged tissue.

The use of stem cells means that with one clonal cell line it is possible to repair damage in a number of different areas of the brain. It also means that if more than one particular cell type is required to repair damage in a given area then a single cell line will be capable of differentiating into the different types of cells required.

Conditionally immortal cells are cells which are immortal under certain permissive conditions but are not immortal under nonpermissive conditions. In the present case this means that by conditionally immortalising the stem cells and maintaining them under permissive conditions the development of the stem cells may be arrested at a

The treatment may be carried out on any mammal but the present invention is especially concerned with the treatment of humans, especially treatment with human cells, and with human cells and cell lines.

The cells of the present invention are capable of correcting a behavioural or psychological deficit when implanted into a damaged part of the human brain. The term "damage" used herein includes reduction or loss of function. Damage may be caused by any of a variety of means including physical trauma, hypoxia (lack of oxygen), chemical agents, for example, damage may be caused by drug abuse, and disease. The following diseases and pathological conditions are examples of diseases or conditions which result in behavioural and/or psychological deficits which may be treated in accordance with the present invention: traumatic brain injury, stroke, perinatal ischaemia, including cerebral palsy, Alzheimer's, Pick's and related dementing neurodegenerative diseases, multi-infarct dementia, Parkinson's and Parkinson's type diseases, Huntington's disease, Korsakoff's disease and Creuzfeld-Jacob disease. Amnesia, particularly following transitory global ischaemia such as after cardiac arrest or coronary bypass surgery, may also be treated in accordance with the present invention.

The cells may also be administered to sites distant from the actual site of damage, for example, the cells may be administered to the contra-lateral region from that exhibiting damage.

The present invention provides for the use of haematopoietic stem cells, optionally in isolated form, in the manufacture of a medicament for the treatment of a behavioural and/or psychological deficit. The medicament to be administered comprises haematopoietic stem cells.

The present invention further provides for the use of conditionally immortal, haematopoietic stem cells in the manufacture of a medicament for the treatment of a behavioural and/or psychological deficit. The medicament to

TRANSPLANTATION

Field of the Invention

The present application relates to the correction of behavioural and/or psychological deficits by the intracerebral transplantation of stem cells, and to cells and medicaments therefor.

Background to the Invention

Behavioural and/or psychological deficits are caused by many diseases and may also be caused when the brain undergoes trauma. For example, motor dysfunction is one symptom of Parkinson's disease. As yet, in most cases, there is no satisfactory treatment available.

Bjornson et al., Science (1999) 283: 534-537, describes the ability of neural stem cells to produce a variety of blood cell types, including myeloid, lymphoid and haematopoietic cells. It is believed that the neural stem cells contain appropriate mechanisms required to express otherwise silent genetic information to respond to signals that normally stimulate blood stem cells. The experiment suggests that the adult blood system contains powerful signals that "activate" the neural stem cells.

Summary of the Invention

The present invention is based in part on the observation that, when transplanted into a damaged or diseased brain, haematopoietic stem cells appear to respond to signals from the damaged or diseased brain by taking up a phenotype that is able to replace or compensate for functional deficits to which the damage or disease otherwise leads.

For use in the present invention the haematopoietic stem cells should be capable of differentiating into cells appropriate to repair or compensate for the damage or disease in the target area of the brain. It will be appreciated that cells for transplantation need not be capable of differentiation into all types or phenotypes of neural cells.